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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/829,250	04/22/2004	Noriaki Hattori	252040US0C0CONT	8196
22850	7590	10/04/2006	EXAMINER	
C. IRVIN MCCLELLAND OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C. 1940 DUKE STREET ALEXANDRIA, VA 22314			SLOBODYANSKY, ELIZABETH	
			ART UNIT	PAPER NUMBER
			1652	

DATE MAILED: 10/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/829,250

Applicant(s)

HATTORI ET AL.

Examiner

Elizabeth Slobodyansky, PhD

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 September 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 14-34 is/are pending in the application.
- 4a) Of the above claim(s) 25-31, 33 and 34 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 14-24 and 32 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement. _____

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 22 April 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☒ Certified copies of the priority documents have been received in Application No. 09/581,241.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>4/22/04; 5/11/06; 9/18/06</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This application is a continuation of application 09/581,241 now US Patent 6,812,012.

Claims 14-34 are pending.

Election/Restrictions

Applicant's election with traverse of Group I, claims 14-24 and 32, in the reply filed on September 7, 2006 is acknowledged. The traversal is on the ground(s) that "for restriction to be proper, there must be undue burden of examination imposed by examination of the claims in the application. Applicants note that, in this instance, all of the claims are classified in class 435. Furthermore, Applicant submit that all of the claims include a particular technical feature, i.e. mutation of a luciferase such that the enzyme maintains activity in the presence of a surfactant, such that search of this feature would reveal all relevant prior art. Thus, no undue burden of search is imposed by search of all of the claims of the present application" (Remarks, page 2). This is not found persuasive because the fact that all the claims are classified in class 435 does not make the search of the prior art any easier because said class comprises a great number of subclasses and covers the diverse subject matter. In the restriction requirement only the most comprehensive class/subclass is indicated. Thus, the search of Group II would require in addition to the search of class 435, subclass 252.3 the search of at least class 435, subclass 320.1 and class 536, subclass 23.2. In addition, in order to make an adequate examination, the text search of the patent and non-patent

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literature is necessary. While the search for different Groups would overlap, additional considerations are required for the examination of different Groups.

The requirement is still deemed proper and is therefore made FINAL.

Claims 25-31, 33 and 34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected Groups II-IV, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on September 7, 2006.

Information Disclosure Statement

The reference on the information disclosure statement filed September 18, 2006 is lined through because there is no sufficient information to identify the reference.

It was rewritten in the correct format on form PTO-892.

Claim Objections

Claim 18 is objected to because it recites "a luciferase" where "the native luciferase" appears to be appropriate.

Claim 32 is objected to as dependent from non-elected claim 28. In the interest of the compact prosecution claim 32 was construed as it were properly written, i.e. included all the limitations of claim 28.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-24 and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 14 is directed to a mutant luciferase of any structure and properties having at least one amino acid mutation and having resistance to a surfactant, wherein said luciferase retains at least 85% of its activity in the presence of 0.1% surfactant improved luciferase activity in the presence of a surfactant compared to a native luciferase. Claims 15-17 depend from claim 14 and limit surfactant to a cationic, a quaternary ammonium salt and a benzalkonium chloride, respectively. Claims 18-22 depend from claim 14 and limit the source of the native luciferase. Claim 24 depends from claim 14 limits the mutation to the mutation at the position corresponding to position 490 of the GENJI or HEIKI firefly luciferase. Claim 32 is drawn to a surfactant resistant luciferase produced by the method of claim 28. Since the patentability of the product resides in the product, the luciferase of claim 28 is equivalent to luciferase of claim 14 for the purposes of this rejection.

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Claim 18 depends from claim 14, where the native luciferase derived from Order Cleoptera. Claim 19 depends from claim 14 and limits the native luciferase to the family firefly. Claim 20 depends from claim 14 and limits the native luciferase to the family *Pyrophorus*. Claim 21 depends from claim 14 and limits the native luciferase to GENJI firefly, HEIKE firefly, North American firefly or Russian firefly. Claim 22 depends from claim 14 and limits the native luciferase to the derived from *Pynophorous plagiophthalmus*, *Arachnocampa luminosa* or Rail worm. Order Cleoptera includes several Families of organisms having different physiological and biochemical properties, which in turn comprise several genera of organisms having different physiological and biochemical properties.

Claims 23 does not limit the number of possible mutation while claim 24 while referring to the luciferase from *Luciola lateralis* (HEIKE) or *Luciola cruciata* (GENJI), does not impart any limitation on the structure except for the mutation at position 490. Thus, the claims are drawn to or depend from an enormous genus of a mutant luciferase having at least 85% activity in the presence of a surfactant compared to the parent luciferase. Said genus of mutants is characterized by function.

Applicants disclose two mutants of *L. lateralis* luciferase having an improved activity in the presence of a surfactant having sequences of SEQ ID NOs: 4 and 6 that comprise mutation E490K. (These two sequences differ by the mutation at 217 wherein SEQ ID NO:4 has A217L and SEQ ID NO:6 has A217I). Therefore, a representative number of a luciferase mutated at position 490 is two. Moreover, the specification fails to describe any other representative species by any identifying characteristics or

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properties other than the "functionality" of having an improved activity in the presence of a surfactant and fails to provide any structure: function correlation present in all members of the claimed genus. Therefore, the specification is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Claims 14-24 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for mutant *Luciola lateralis* luciferases having the sequences of SEQ ID NO:4 or SEQ ID NO:6 that are mutated at position 490 and have at least 5% activity in the presence of a surfactant compared to the native luciferase, mutant *Luciola cruciata* luciferases with corresponding sequences, does not reasonably provide enablement for a mutant luciferase having an unknown homology to SEQ ID NO:4 or SEQ ID NO:6 and having at least 85% activity in the presence of 0.1% surfactant compared to the native luciferase, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, how to make the invention commensurate in scope with these claims.

Claim 14 is directed to a mutant luciferase of any structure and properties (the number of possible mutations is not limited) having improved luciferase activity in the presence of a surfactant compared to a luciferase in which a mutation has not been introduced. Claims 14-24 and 32 are so broad as to encompass any mutant

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luciferase with an unknown possible low homology to the luciferase of *Luciola lateralis* having the requisite properties or any mutant luciferase with an unknown possible low homology to the luciferase of *Luciola lateralis* having the requisite properties in which the amino acid corresponding to residue 490 is substituted. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of mutant luciferase enzymes broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and amino acid sequence of two mutant luciferases having one or two amino acids different compared with the wild-type sequence.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional

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modification, i.e. multiple substitutions. The specification does not support the broad scope of the claims which encompass any mutant luciferase having the requisite property with an undisclosed homology to the luciferase of *Luciola lateralis* and any mutant luciferase with no or low homology to the luciferase of *Luciola lateralis* in which the amino acid corresponding to residue 490 of *Luciola lateralis* luciferase is mutated because the specification does not establish: (A) regions of the protein structure which may be modified without effecting luciferase activity; (B) the general tolerance of luciferases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any luciferase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any luciferase with no or low homology to the luciferase of *Luciola lateralis* having the desired properties in which the amino acid corresponding to residue 490 is or is not mutated. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of luciferases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

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The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18-22 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 18-22 are confusing because they are drawn to the luciferase of claim 14 deprived from the natural source whereas claim 14 is drawn to a mutant luciferase. There is a contradiction between the claimed luciferase being a mutant and at the same time being derived from a native organism.

Claim 24 is indefinite for the recitation of the 490 amino acid position without indicating a sequence identifier of the sequence where said position is located.

Reference to SEQ ID NO: of a wild-type luciferase would obviate this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting

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directly or indirectly from an international application filed before November 29, 2000.

Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 14-21, 23, 24 and 32 are rejected under 35 U.S.C. 102(e) as being anticipated by Hirokawa et al.

The applied reference has a common assignee and one common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Hirokawa et al. (US Patent 6,074,859, form PTO-1449 filed April 22, 2004) teach mutant luciferases having improved activity compared with the wild type luciferase. The activity is measured in buffers containing surfactants such as HEPES, CHES, Mes, TAPS, ammonium sulfate, etc (for example, columns 12-13). Furthermore, Hirokawa et al. teach SEQ ID NO: 14 that has 99.8% identity to SEQ ID NO:4 and 99.7% identity to SEQ ID NO: 6 of the instant invention. SEQ ID NO:4 of the instant invention differs from SEQ ID NO:14 disclosed in the Hirokawa et al. patent only by substitution T2191. SEQ ID NO:6 of the instant invention differs from said sequence by two substitutions L2171 and T2191. Both Hirokawa et al. sequences have E490K substitution. Said mutant luciferase has an improved activity compared with the wild-type luciferase in buffers

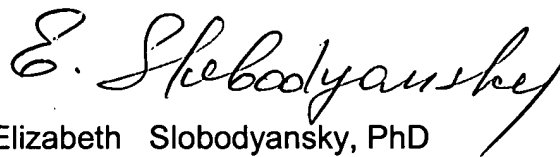
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containing surfactants. Hirokawa et al: teach methods for measuring ATP using luciferase (Example 5).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652

September 26, 2006